

Trends in U.S. Pleural Mesothelioma Incidence Rates Following Simian Virus 40 Contamination of Early Poliovirus Vaccines

Howard D. Strickler, James J. Goedert, Susan S. Devesa, John Lahey, Joseph F. Fraumeni, Jr., Philip S. Rosenberg

Background: Poliovirus vaccines that were used during the late 1950s and early 1960s were contaminated with simian virus 40 (SV40), a monkey virus that is tumorigenic in rodents. SV40 DNA sequences have been detected in some human cancers, especially pleural mesotheliomas, although results are conflicting. We examined the relationship between SV40-contaminated poliovirus vaccine exposure and subsequent rates of pleural mesothelioma in the United States. **Methods:** We used data from the Surveillance, Epidemiology, and End Results Program to estimate age- and sex-specific pleural mesothelioma incidence rates per 10⁵ person-years (py) from 1975 through 1997 and the Poisson distribution to determine 95% confidence intervals (CIs) for each rate. The prevalence, by birth cohort, of poliovirus vaccine exposure during the period of widespread SV40 contamination was determined from published survey data. Trends in mesothelioma incidence rates were assessed by examining age- and sex-specific rates over calendar periods and with the use of the age-period-cohort model. Trends in mesothelioma incidence were then compared with trends in prevalence of exposure. All statistical tests were two-sided. **Results:** The age-standardized pleural mesothelioma incidence rate for 1975 through 1997 was 1.29/10⁵ py (95% CI = 1.24/10⁵ to 1.34/10⁵ py) in males and 0.21/10⁵ py (95% CI = 0.20/10⁵ to 0.23/10⁵ py) in females. The rate in males increased from 0.79/10⁵ py (95% CI = 0.62/10⁵ to 1.0/10⁵ py) in 1975 to a peak of 1.69/10⁵ py (95% CI = 1.46/10⁵ to 1.95/10⁵ py) in 1992. Incidence rates increased the most among males who were 75 years of age or older, the age group least likely to have been immunized against poliovirus. Incidence rates among males in the age groups most heavily exposed to SV40-contaminated poliovirus vaccine remained stable or decreased from 1975 through 1997. Similar age-specific trends were observed among females. The age-period-cohort models for men and women also indicated that the trends in pleural mesothelioma incidence were not related to trends in exposure to SV40-contaminated poliovirus vaccine. **Conclusions:** Age-specific trends in U.S. pleural mesothelioma incidence rates are not consistent with an effect of exposure to SV40-contaminated poliovirus vaccine. Nonetheless, given reports of the detection of SV40 genomic DNA sequences in human mesotheliomas, monitoring of vaccine-exposed cohorts should continue. [J Natl Cancer Inst 2003; 95:38–45]

Simian virus 40 (SV40), an agent that infects Asian macaques, contaminated the early poliovirus vaccines used in the United States, Europe, and other regions during the late 1950s and early 1960s (1). SV40 was discovered in 1960 (2), and evidence of its oncogenicity in rodents was reported in 1961 (3).

That same year, the U.S. government required that all newly manufactured poliovirus vaccine be free of SV40. However, previously produced vaccine was not removed from the mass immunization program and, considering its possible storage for up to 1 year and its 6-month shelf life, SV40-contaminated poliovirus vaccine was likely in widespread use in the United States from the start of the mass immunization program in 1955 through 1963 (1).

The mass immunization program was initially targeted to first- and second-graders (who were approximately 6–8 years of age), then more broadly to children 5–9 years of age, persons younger than 20 years, and pregnant women (4). As vaccine availability improved, other groups were also immunized but not as extensively as those initial groups. The U.S. population was repeatedly surveyed during the mass immunization program to assess the coverage of the program (5). Data from those surveys now provide reliable information regarding the prevalence (probability) of poliovirus vaccine exposure, by year of birth, during the period of widespread SV40 contamination of the vaccine. In 1961, contemporaneous surveys indicated that approximately 90% of U.S. citizens younger than 20 years of age (i.e., those born from 1941 through 1961) had received at least one immunization with poliovirus vaccine. As shown in Fig. 1, the rate of exposure to potentially SV40-contaminated vaccine decreased with increasing age. Individuals who were 50 years of age or older in 1961 (e.g., those born prior to 1912) had a less than 10% prevalence of poliovirus immunization, and persons born prior to 1902 were unlikely to have ever been vaccinated.

Further characterization of exposure to SV40-contaminated poliovirus vaccine on an individual basis is impossible, because necessary information about the titer of live SV40 in individual vaccine lots is unavailable, and vaccinees typically received multiple immunizations (a standard course of vaccination was a series of three injections and a booster) (5). A frequently cited review of the available data indicates that titers of live SV40 in specific vaccine lots varied from undetectable to high. However, because each vaccinee received multiple immunizations, the reported data suggest that most U.S. citizens who were vaccinated between 1955 and 1963 had at least one exposure to live SV40 (1).

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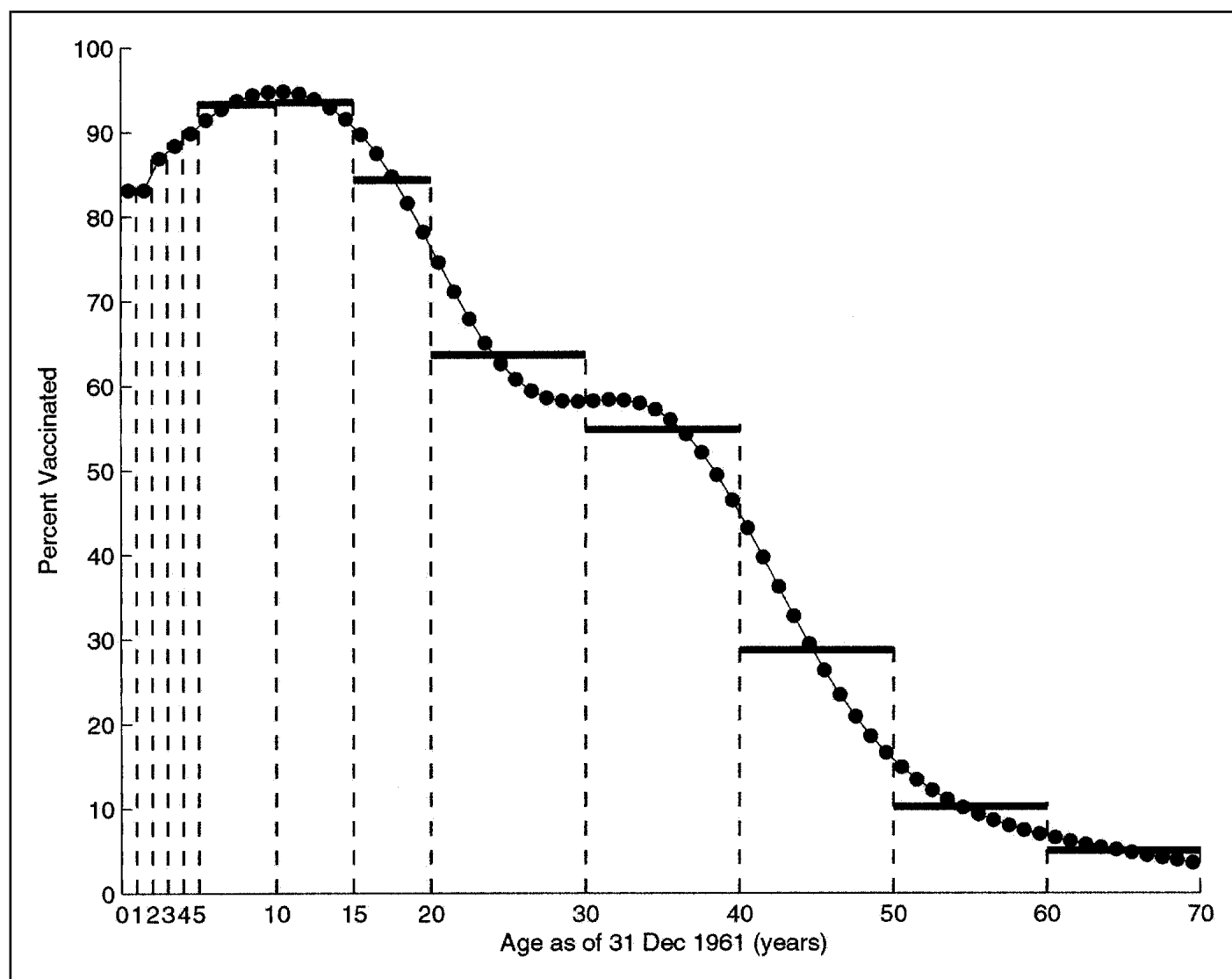


Fig. 1. The age-specific prevalence of exposure to potentially SV40-contaminated poliovirus vaccine in the United States in 1961. **Solid horizontal bars** represent the raw 1961 data reported by the Bureau of the Census, which were based on their annual national household sample surveys. The values shown on the **dotted curve** for ages 1–5 also represent raw data, whereas the remainder of the **dotted curve** represents estimates by single year of age determined by using a cubic smoothing spline. The sum of the smoothed age-specific prevalences exactly matches what was observed in the survey.

Most epidemiologic studies of population groups that were immunized with potentially SV40-contaminated poliovirus vaccines during early childhood, the most vulnerable period for exposure according to animal models, have failed to detect any association of immunization with increased risks of cancer, even more than 30 years following exposure (6–12). However, an increasing number of DNA hybridization studies that have used polymerase chain reaction amplification have reported the detection of SV40 DNA sequences in certain human cancers (12). Most such reports have involved brain tumors in children (13,14); osteosarcomas, which mainly affect teenagers and young adults (15,16); and pleural mesotheliomas, which generally occur in adults older than 50 years (17–24).

Pleural mesothelioma has been the tumor most often reported to contain SV40 DNA (12,17–24), although there are also a small but growing number of studies (25–28) that have not detected the virus in pleural mesothelioma specimens. Mesothelioma is strongly linked to asbestos exposure, with approximately 60%–80% of cases having evidence of past exposure to asbestos

(29). Mesothelioma incidence rates are higher among individuals who have had occupations that involved extensive use of asbestos, such as shipbuilding, as well as in the communities where these industries have been centered (29,30).

Previous epidemiologic investigations that examined the risks of cancer associated with exposure to SV40-contaminated poliovirus vaccine focused on birth cohorts that were of appropriate ages for the analysis of childhood brain cancer and osteosarcoma but that were young relative to the age groups that account for most cases of pleural mesothelioma. In addition, reports of SV40 DNA detection in pleural mesothelioma specimens have typically involved patients who were adults during the late 1950s and early 1960s, but little attention has been paid to the potential cancer risks associated with adult exposure to SV40-contaminated poliovirus vaccine. Therefore, we examined pleural mesothelioma incidence trends among adults in various age groups in relation to the probability of their exposure to potentially SV40-contaminated poliovirus vaccine between 1955 and 1961.

MATERIALS AND METHODS

Prevalence of Exposure

Participation in the nationwide Salk poliomyelitis inoculation program was monitored by national household sample surveys that were conducted annually by the Bureau of the Census (1,5). Available data from the 1961 survey provide nationally representative estimates of the number of persons in the United States who had received at least one dose of poliovirus vaccine during the period of its widespread contamination with SV40 for the following age groups: less than 1 year, 1 year, 2 years, 3 years, 4 years, 5–9 years, 10–14 years, 15–19 years, 20–29 years, 30–39 years, 40–49 years, and 50–59 years. Because the participation rate among persons younger than 1 year of age reflected a midyear value (i.e., many infants born in 1961 were born after the survey was conducted or had not yet received their first vaccination), we assumed that the participation rate among persons younger than 1 year of age was equal to the value reported for persons who were 1 year of age at the time of the survey. Because data were not reported for those individuals who were 60–70 years of age, we assumed that participation rates continued to decline with age and used 5%, the midpoint value between 0% and 10% (the rate for those aged 50–59 years), as the rate of participation for the 60- to 70-year-old age group. Trends in exposure by single-year birth cohorts were derived from these data as follows. A step function was plotted to describe the prevalence of inoculation by age group. The step function was smoothed by using a cubic smoothing spline constrained to match the area under each step. The resulting smoothed curve provided estimates of prevalence by single year of age. The smoothed curve was obtained by the use of a sequential quadratic programming algorithm (the QUADPROG function in the Optimization Toolbox for Matlab: The Language of Technical Computing Version 6.0, 2002; The MathWorks Inc., Natick, MA) and has the following properties: Within each age group, the sum of the smoothed age-specific prevalences matched the values that were observed in the survey exactly; this curve is the smoothest function that does so.

Rates and Trends

We used the International Classification of Diseases for Oncology (ICD-O) site code 384 and histology codes 9050, 9051, 9052, 9053, 9054, and 9055 (31) to obtain pleural mesothelioma incidence data from the Surveillance, Epidemiology, and End Results (SEER)¹ Program of the National Cancer Institute (32). Since 1973, SEER has collected detailed information on new cancer cases that are reported to qualified population-based tumor registries, and since 1975, SEER has comprised a representative sample of approximately 10% or more of the U.S. population. The SEER Program uses extensive quality-control procedures, which include the rigorous training of abstractors and coders, sample re-abstracting, and the review of case findings. The Manual of Tumor Nomenclature and Coding (33), which was used by SEER in the early years to code tumors, made a distinction between pleural mesothelioma cases reported to be malignant and those not specified as malignant, and both sets of cases were recorded in the SEER database. However, this distinction was eliminated with adoption of the International Classification of Diseases for Oncology (34) in 1976. Inspection of the annual number of cases did not reveal a surge around

1977, suggesting that the change in coding practices did not affect case reporting.

The current analyses were limited to cases of pleural mesothelioma, because almost all reports of the detection of SV40 DNA in mesotheliomas have specifically involved pleural tumors. Annualized age- and sex-specific cancer incidence rates from 1975 through 1997 were calculated with the use of data from all SEER sites that were active since 1975 (i.e., those in the San Francisco Bay area, the Puget Sound area of Seattle, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Utah, and Atlanta) and of population demographic data from the U.S. Bureau of the Census. Age-standardized incidence rates were determined using the U.S. population distribution in 1970 as the standard, and 95% confidence intervals (CIs) for all incidence rates were calculated on the basis of the Poisson distribution. The estimated annual percent change in age-standardized rates was determined with the use of a simple regression model in which the outcome was the log (age-standardized incidence rate), the independent variable was time, and weight was the number of cases.

Age-Period-Cohort Model

We used the age-period-cohort model (35) to estimate the expected incidence rate of pleural mesothelioma as a function of age, calendar year, and birth cohort. The model simultaneously accounts for birth-cohort effects, effects associated with aging, and temporal trends that may have impacted all age groups in the population at once. These latter “period effects” most often reflect changes in screening or diagnostic practice. Formally, the model expresses the logarithm of the incidence rate as a sum of an age-group effect, a calendar-period effect, and a birth-cohort effect. However, because the linear trends in calendar period and birth cohort are necessarily confounded, we based our inferences on two sets of estimable functions (i.e., contrasts) of the birth-cohort effects. These contrasts were designed to measure changes in the trend of the birth-cohort effects, which are also called “slope contrasts” or “curvature effects.” The first set of functions of the birth-cohort effects estimated changes in the linear slope of the birth cohort effects that spanned approximately 10 years and that covered periods during which the cohort-specific vaccine prevalence curve was approximately linear, specifically 1894 through 1899, 1900 through 1907, 1908 through 1917, 1918 through 1927, 1928 through 1935, 1936 through 1947, and 1948 through 1957. The second set of functions of the birth cohort effects contrasted consecutive differences of 2-year birth cohorts: 1900 through 1901, 1902 through 1903, and so on up to 1960 through 1961; these differences are unique up to an arbitrary constant.

Slope contrasts measured whether the birth-cohort effects were accelerating or moderating over birth year. In general, acceleration indicated either that a rate was increasing or that a decreasing rate was decreasing less quickly. Moderation indicated either that a rate was decreasing or that an increasing rate was increasing less quickly. We examined the first (i.e., 10-year) set of contrasts specifically for evidence of acceleration in birth cohorts that were exposed to potentially SV40-contaminated poliovirus vaccine as adults. We examined the second (i.e., 2-year) set of contrasts for evidence that respective differences in cohort effects were related to corresponding differences in the prevalence of exposure. In this latter analysis, we calculated the slope of the regression line between changes in cohort effects and changes in prevalence of exposure. Because the variances of

individual cohort effects were different, we weighted each contrast by the inverse of its estimated variance. All statistical tests throughout the analyses were two-sided.

RESULTS

Prevalence of Exposure

Between 1955 and 1961, more than 90% of school-age children had been inoculated with at least one dose of poliovirus vaccine (Fig. 1). More than 60% of persons in their 20s and more than 50% of persons in their 30s had also been vaccinated.

Rates and Trends

On the basis of 525 million person-years (py) of follow-up data in SEER, we found that pleural mesothelioma was uncommon from 1975 through 1997 (Fig. 2, A). The overall age-adjusted incidence rate was $0.67/10^5$ py (95% CI = $0.65/10^5$ to $0.69/10^5$ py), and the rate in males ($1.29/10^5$ py, 95% CI = $1.24/10^5$ to $1.34/10^5$ py) was sixfold higher than the rate in females ($0.21/10^5$ py, 95% CI = $0.20/10^5$ to $0.23/10^5$ py).

Among males, there was a statistically significant upward trend in the age-adjusted rates of pleural mesothelioma over time; those rates increased from $0.79/10^5$ py (95% CI = $0.62/10^5$ to $1.0/10^5$ py) and $0.84/10^5$ py (95% CI = $0.66/10^5$ to $1.05/10^5$ py) in 1975 and 1976, respectively, to a peak of $1.69/10^5$ py (95% CI = $1.46/10^5$ to $1.95/10^5$ py) in 1992. After 1992, pleural mesothelioma incidence rates in males appeared to plateau or even to decrease, with rates in 1996 and 1997 of $1.45/10^5$ py (95% CI = $1.24/10^5$ to $1.68/10^5$ py) and $1.26/10^5$ py (95% CI = $1.07/10^5$ to $1.48/10^5$ py), respectively. The overall average rate of increase for males for the period from 1975 through 1997 was 3.25% per year (95% CI = 2.41% to 4.09% per year). Similarly, pleural mesothelioma incidence rates among females increased

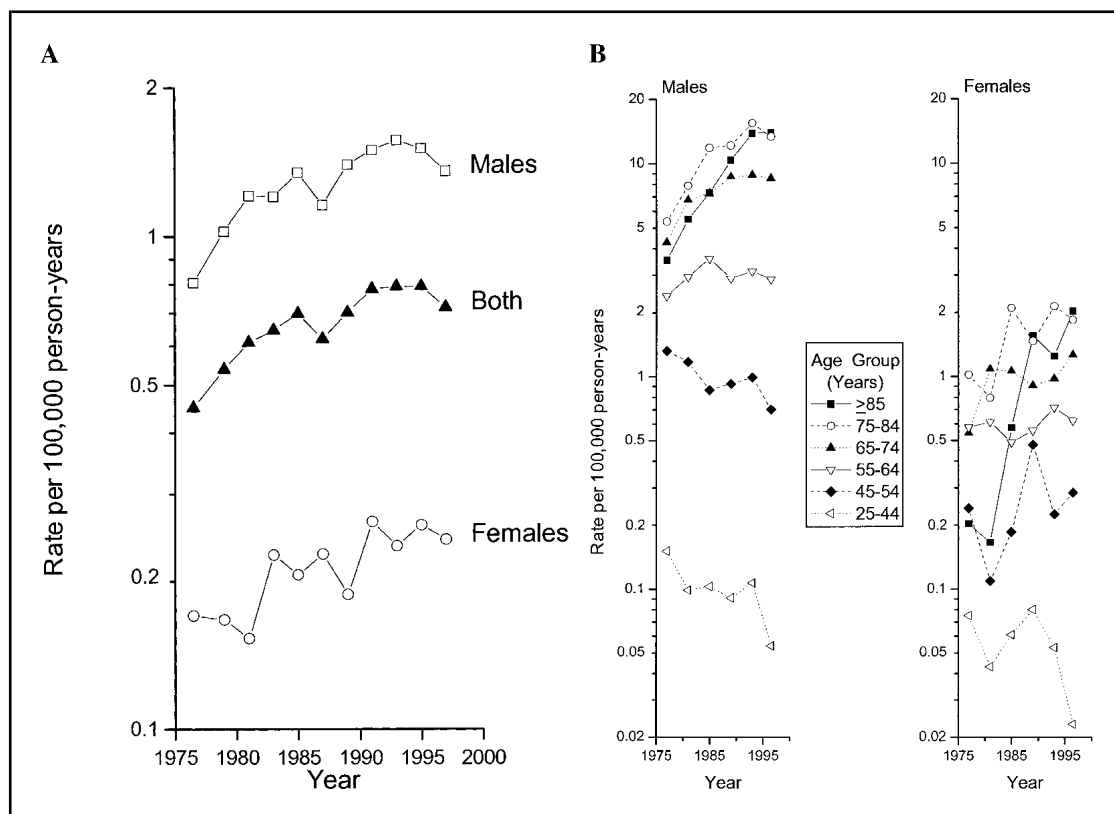
approximately 2.99% per year (95% CI = 1.92% to 4.08% per year) during the period of observation, from $0.13/10^5$ py (95% CI = $0.07/10^5$ to $0.22/10^5$ py) and $0.21/10^5$ py (95% CI = $0.13/10^5$ to $0.32/10^5$ py) in 1975 and 1976, respectively, to $0.26/10^5$ py (95% CI = $0.18/10^5$ to $0.36/10^5$ py) and $0.23/10^5$ py (95% CI = $0.16/10^5$ to $0.32/10^5$ py) in 1996 and 1997, respectively. The absolute number of cases in females remained low, however. From 1991 through 1997, for example, there was an average of only 38 cases in females each year among the approximately 13 million females in SEER, compared with an average of 177 cases in males diagnosed each year among the approximately 12 million males in the SEER database.

The greatest increases in pleural mesothelioma incidence occurred among men and women in the two oldest age groups (i.e., ages 75–84 years and ≥ 85 years), who were the least likely to have been exposed to SV40-contaminated poliovirus vaccine (Fig. 2, B). For example, a man who was 85 years old in 1979 or 1980, when the initial large increases in mesothelioma incidence occurred, would have been 66 years old in 1961, and his probability of exposure to SV40-contaminated vaccine was less than 5%. A man who was 85 years old in 1991 or 1992, when mesothelioma rates peaked, would have been 54 years old in 1961, and the probability of his exposure to SV40-contaminated vaccine was approximately 10%. By contrast, rates of mesothelioma among the much more heavily exposed birth cohorts (i.e., those in the 25- to 44-year and 44- to 54-year age groups) remained stable or decreased between 1975 and 1997.

Age-Period-Cohort Model

To further examine these relationships, we applied age-period-cohort regression models to the pleural mesothelioma incidence data for males and females, which were tabulated by single year of age (for ages 30–84 years) and by period (for

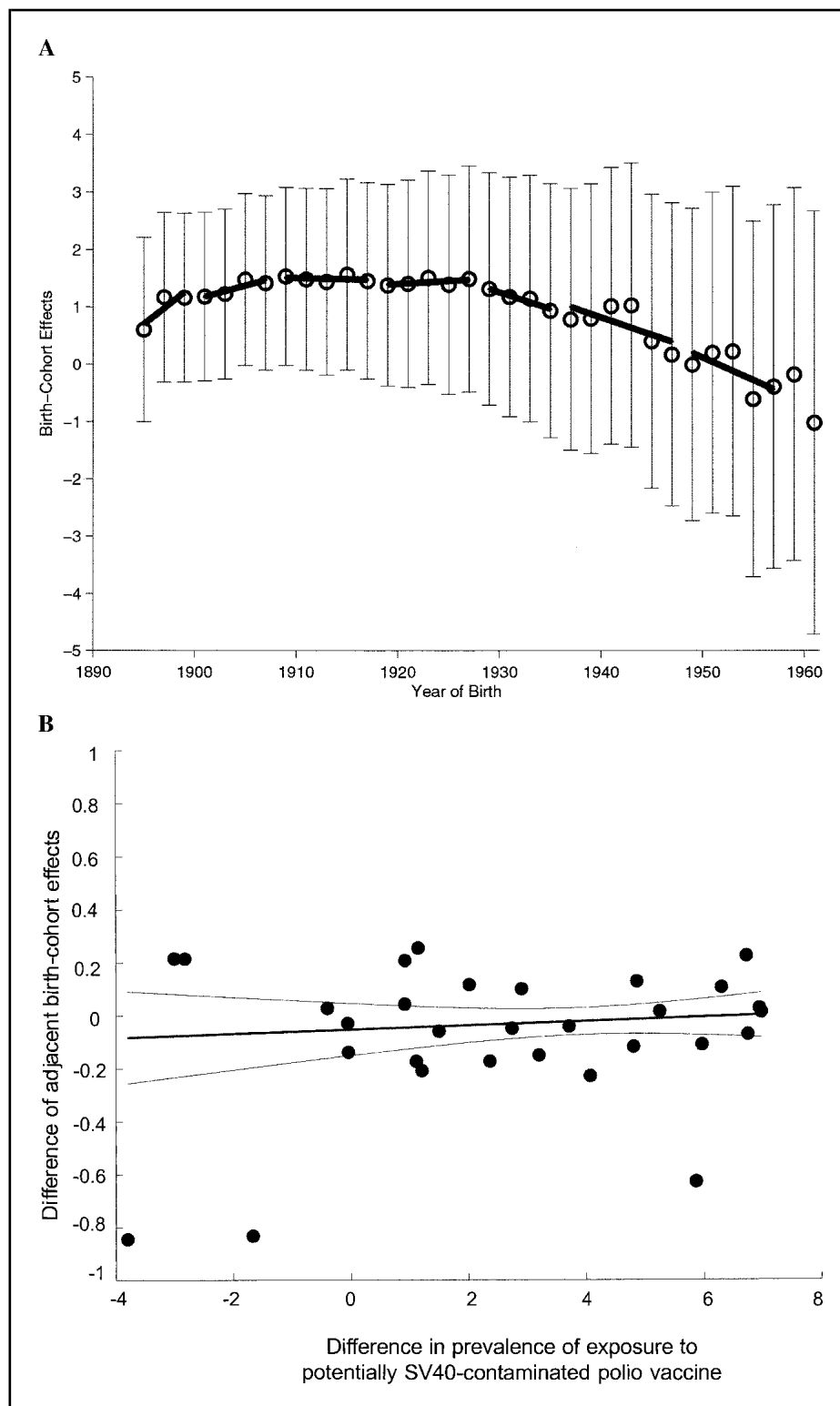
Fig. 2. Pleural mesothelioma incidence rates in the United States based on data from the Surveillance, Epidemiology, and End Results Program. **A)** Age-standardized pleural mesothelioma incidence rates in males, females, and both combined for 3-year periods 1975–1977 through 1993–1995, and 1996 through 1997. **B)** Age-specific pleural mesothelioma incidence rates in males and females for 4-year periods 1975–1978 through 1991–1994, and 1995–1997. Longer time units were used with the age-specific rates because of the small number of observations in any individual age stratum.



calendar years 1975 through 1997). Among men, there were 130.1 million py of observation and 2928 incident cases of pleural mesothelioma. The observed and expected incidence rates were similar (the chi-square statistic for deviance was 1215.6 and was approximately equal to the degrees of freedom, which numbered 1190). One set of the estimated birth-cohort effects in men is shown in Fig. 3, A. These estimates were obtained by fitting step functions for age, period, and birth cohort with 2-year steps (the 1890 through 1891 and 1892 through 1893 birth-

cohort effects were set equal to each other because of the very low rate of exposure and low incidence in early birth cohorts). Slope contrasts are superimposed on this particular model; the differences between the slope contrasts are estimable, because they are invariant to the choice of the identifiability constraints that were used to fit the model. The slope contrasts show that there was a marked and statistically significant decrease in risk of pleural mesothelioma for males born from 1928 through 1935 compared with the risk for those born from 1918 through 1927

Fig. 3. Birth-cohort effects in men. **A)** Birth-cohort effects and slope contrasts, as estimated by the age-period-cohort model. **Vertical bars** represent 95% confidence intervals (CIs) for each birth-cohort effect (indicated by **circles**), based on 2-year sets of contrasts: 1894–1895, 1896–1897, and so on up to 1960–1961 are shown. **Solid dark lines** represent slope contrasts, which measure whether the birth-cohort effects are accelerating (upward slope) or moderating (downward slope). In general, acceleration indicates either that a rate is increasing or that a decreasing rate is decreasing less quickly. Moderation indicates either that a rate is decreasing or that an increasing rate is increasing less quickly. **B)** Differences between adjacent 2-year birth-cohort effects in relation to the differences in prevalence of exposure to potentially SV40-contaminated poliovirus vaccine. Individual data points are plotted as **solid circles**. Ordinates equal the differences between adjacent 2-year birth-cohort effects (i.e., 1902–1903 versus 1900–1901, 1903–1904 versus 1902–1903, and so on), and abscissas equal the corresponding differences in the prevalence of exposure to potentially SV40-contaminated vaccine. The **dark horizontal line** is the weighted regression line between the changes in cohort effects and changes in prevalence of exposure, and the upper and lower **curved lines** indicate the 95% CIs for the regression line. A positive association between SV40 exposure and incidence of mesothelioma would be indicated by increasing positive differences in adjacent birth-cohort effects with increasing differences in the prevalence of exposure to SV40-contaminated vaccine (i.e., a line with a positive slope).



(Table 1). The difference between the slopes for the 1928–1935 and the 1918–1927 birth cohorts was $-.068$ (95% CI = $-.122$ to $-.015$) (P value for Wald test = $.013$). No other slope contrasts for males were statistically significant. These results suggest that the moderation in risk that started with the 1928–1935 birth cohorts continued in the subsequent birth cohorts, despite the much greater exposure of the subsequent birth cohorts to SV40-contaminated vaccine.

We also examined short-term (i.e., 2-year) changes in birth-cohort effects and assessed the association between those changes and trends in the prevalence of exposure to SV40-contaminated vaccine. The findings for males are summarized in Fig. 3, B. As shown, the ordinates equal the difference between adjacent (i.e., 2-year) birth-cohort effects (for example, 1902–1903 versus 1900–1901 and 1903–1904 versus 1902–1903), and the abscissas equal the corresponding differences in the prevalence of exposure to potentially SV40-contaminated vaccine. The slope of the weighted regression line did not differ statistically significantly from zero (slope = 0.0076 , standard error = 0.011 , $P = .49$). Thus, short-term changes in birth-cohort effects were not related to short-term changes in rates of vaccine exposure. The results among females were similar, except that a statistically significant moderation in risk was observed earlier among females, beginning with the 1918–1927 birth cohort, than it was among males (Table 1). As in males, there was no association in females between the short-term changes in birth-cohort effects and changes in the probability of exposure to SV40-contaminated poliovirus vaccine; i.e., the slope of the weighted regression line for the 2-year contrasts was not statistically significantly different from zero (slope = -0.0096 , standard error = 0.0253 , $P = .70$).

DISCUSSION

SV40 contaminated the poliovirus vaccines used during the late 1950s and early 1960s, causing the largest single-source exposure of humans to this tumorigenic monkey virus (1). By 1961, most U.S. citizens under the age of 40 years had been injected with poliovirus vaccine that potentially contained live SV40. In the past few years, an increasing number of polymerase chain reaction-based studies have reported the detection of SV40 genomic DNA sequences in pleural mesothelioma tumor samples (17–24), raising concerns that exposure to contaminated

vaccine might have caused human infection with SV40, which in turn might have led to the development of these tumors (12). To assess the relationship between SV40-contaminated poliovirus vaccine exposure and subsequent rates of pleural mesothelioma, we studied cancer incidence data from SEER, which comprises a representative sample of approximately 10% of the U.S. population, and nationwide prevalence rates of poliovirus vaccine immunization between 1955 and 1961.

The data show that pleural mesothelioma has remained an uncommon tumor, with an incidence of less than one case per 100 000 py and a sixfold predominance in males versus females. The persistent rarity of pleural mesothelioma among women, whose average incidence of the disease is $0.21/10^5$ py, is noteworthy because both sexes were exposed to SV40-contaminated poliovirus vaccine in similar numbers. The small number of cases that did arise in women mainly involved those in the oldest age groups, which were the least likely of all the age groups to have ever received the poliovirus vaccine.

The paucity of pleural mesothelioma cases in females, and the lack of an association between cases of the disease and immunization (in either sex), argues against an independent association between pleural mesothelioma and exposure to SV40-contaminated vaccine. Some investigators have suggested that exposure to SV40-contaminated vaccine might have specifically increased the risk of pleural mesothelioma in individuals who were not exposed to asbestos (23). However, our findings suggest that the number of such cases, if any, that might be attributable to SV40-contaminated vaccine exposure would be a fraction of the low number of cases in women plus a similar small number of cases in men. Although it has been speculated that alternative routes of exposure to SV40, such as person-to-person transmission or unrecognized contamination of oral poliovirus vaccines after 1963, might have caused an increased risk of tumors (36), recent studies have challenged the occurrence of such exposures (12,37–40). Moreover, the persistent rarity of pleural mesothelioma in females suggests that, even if alternative exposures to SV40 exist, they did not have a substantial independent effect on the risks of pleural mesothelioma.

Could SV40 represent an etiologic cofactor that interacts with asbestos to cause pleural mesothelioma? An interaction of this type would readily explain the predominance of cases in males, given that men have had much greater occupational exposures to asbestos than women (we are unaware of animal models or other data to suggest any other basis for the sex-related differences in the effects of SV40 exposure on risk of mesothelioma). However, the age-specific incidence trends for pleural mesothelioma in men during recent decades do not suggest an association with SV40-contaminated poliovirus vaccine exposure. In men, as in women, increasing rates occurred most among those in the oldest age groups, which were the least likely to have been exposed to poliovirus vaccine during the period of widespread SV40 contamination, whereas rates in the heavily exposed 25- to 44-year and 45- to 54-year age groups remained stable or decreased over time. In addition, most studies (17–24) that have reported the detection of SV40 DNA in human pleural mesothelioma have failed to detect differences in SV40 prevalence according to asbestos exposure, which would be expected if the putative association of SV40 with pleural mesothelioma was limited to those who were also exposed to asbestos.

Our age-period-cohort model provided a comprehensive statistical assessment of trends in pleural mesothelioma incidence.

Table 1. Ten-year slope contrasts estimated with the use of the age-period-cohort model

Contrasted years	Contrast	95% Confidence interval	P value*
Males			
1948–1957 vs. 1936–1947	-0.018	-0.172 to 0.136	.816
1936–1947 vs. 1928–1935	-0.002	-0.071 to 0.067	.953
1928–1935 vs. 1918–1927	-0.068	-0.122 to -0.015	.013
1918–1927 vs. 1908–1917	0.014	-0.019 to 0.047	.412
1908–1917 vs. 1900–1907	-0.052	-0.115 to 0.012	.110
1900–1907 vs. 1894–1899	-0.091	-0.321 to 0.140	.441
Females			
1948–1957 vs. 1936–1947	0.110	-0.058 to 0.277	.198
1936–1947 vs. 1928–1935	-0.035	-0.169 to 0.010	.614
1928–1935 vs. 1918–1927	-0.009	-0.128 to 0.110	.882
1918–1927 vs. 1908–1917	-0.095	-0.176 to -0.014	.022
1908–1917 vs. 1900–1907	0.090	-0.035 to 0.215	.157
1900–1907 vs. 1894–1899	-0.304	-0.842 to 0.234	.268

* P values were obtained from Wald test.

Among men, birth-cohort effects showed a pattern of moderation in incidence rates, beginning with the 1928–1935 birth cohort, that was consistent with reported trends in occupational exposure to asbestos (29). However, there was no evidence of an acceleration in incidence in subsequent birth cohorts that had higher exposures to SV40-contaminated poliovirus vaccine. The similarity of the observed incidence rates to the expected incidence rates derived by our model suggests that the data were adequately described in the analysis. Similarly, in women, the age–period–cohort model provided no evidence of an acceleration in incidence among birth cohorts that was attributable to exposure to SV40-contaminated poliovirus vaccine.

Our study has three important limitations. First, the absolute number of pleural mesothelioma cases in the United States from 1975 through 1997 was both small and, in recent years, decreasing. Second, we lacked individualized exposure data, including the amount of live virus (most of which was probably low) in each vaccination. Third, trends in incidence that are derived from surveillance data reflect the net impact of all risk factors that affect the population rather than any single effect that might be associated with a calendar period or birth cohort. For all these reasons, cancer incidence trends could fail to detect some effects introduced by exposure to SV40-contaminated poliovirus vaccine.

On the other hand, if an association between vaccine-related SV40 exposure and incidence of pleural mesothelioma was missed because of the limitations of the current analyses, it would appear that the effect was too small to be detected using the best available data in the United States, which consisted of more than 500 million py of observation. Furthermore, our findings are consistent with negative results obtained in previous epidemiologic studies carried out both in the United States and in Europe (6–8,10), as well as with the results of a recent international multilaboratory study (25). In that study, none of nine independent laboratories reproducibly detected SV40 DNA in any of 25 frozen mesothelioma tumor specimens (25).

Our findings are also compatible with a recent survey of U.S. mesothelioma incidence trends, which concluded that the observed variations in mesothelioma rates could be adequately explained by the changing patterns of asbestos exposure (29). Notably, in Sweden, where adults did not receive SV40-contaminated poliovirus vaccine, there has been an upward trend in mesothelioma incidence similar to that observed in the United States (10). A published model (29) of mesothelioma rates for U.S. men predicts that those rates will continue their current decline and eventually reach the very low levels observed in U.S. women.

Thus, after almost 40 years of follow-up, U.S. cancer incidence data have not shown an increased incidence of pleural mesothelioma among the birth cohorts that were exposed to SV40-contaminated poliovirus vaccine. Although the findings have been reassuring to date, continued surveillance of all vaccine-exposed cohorts is needed, in view of conflicting reports on the detection of SV40 genomic DNA sequences in mesothelioma tumor samples.

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NOTES

¹*Editor's note:* SEER is a set of geographically defined, population-based central cancer registries in the United States, operated by local nonprofit organizations under contract to the National Cancer Institute (NCI). Registry data are submitted electronically without personal identifiers to the NCI on a biannual basis, and the NCI makes the data available to the public for scientific research.

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